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Note

Biologically important nucleosides: synthesis of 9-(3,4-anhydro-α-L-talopyranosyl)-6-benzoyladenine

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Adenosine derivatives are known which are antineoplastic agents[1,2] and inhibitors of the adenosine deaminase system that is implicated in several important biological pathways[3,4]. We have been interested in nucleoside derivatives that have an alkylating group in the sugar moiety, and now report a synthesis of the title compound (**6**) with the intention of comparing its biological activity with that of the unsaturated ketonucleosides[5,6], in relation to the hypothesis that these compounds may be active according to their electrophilic properties.

Several syntheses of adenosine analogues have been reported[7,8], involving glycosylation of adenine with suitable sugar derivatives. An alternative route involves modification of the nucleoside; this route has the advantage of allowing biological investigation of the intermediates. The adenosine analogue **6** was obtained by this route.

Lewis acid-catalysed condensation[9] of α-L-rhamnopyranose tetra-acetate with the trimethylsilyl derivative of *N*-benzoyladenine gave the starting material, 6-benzoyl-9-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)adenine (**1**) in good yield. The $J_{1',2'}$ value of <2 Hz indicated the α-L configuration. The currently used deacetylating procedures[10] lack selectivity, but treatment of **1** with dilute ammonium hydroxide cleaved the acetate groups only and gave the desired 6-benzoyl-9-α-L-rhamnopyranosyladenine (**2a**).

The acid-catalysed reaction of **2a** with 2,2-dimethoxypropane gave the 2,3-*O*-isopropylidene derivative **3**, which, with methanesulfonyl chloride in the presence of triethylamine, gave the mesylate **4** in high yield. Methanolysis of **4** with trifluoroacetic acid–methanol[11] (9/1) afforded 6-benzoyl-9-(4-*O*-mesyl-α-L-rhamnopyranosyl)-adenine (**5a**). The n.m.r. signal for H-4 in the sugar moiety of **4** was deshielded (0.9 p.p.m.) compared to the corresponding signal in **3**, thereby confirming the position of the mesyloxy group. Also, H-3 and H-5 in the sugar moiety of **4** were deshielded,

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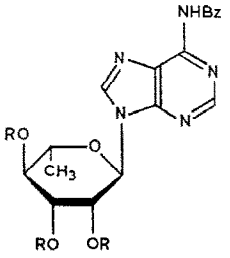
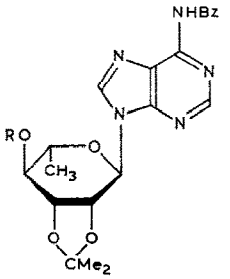
although to a lesser extent (0.55 and 0.2 p.p.m., respectively), probably due to the proximity of the mesyl group.

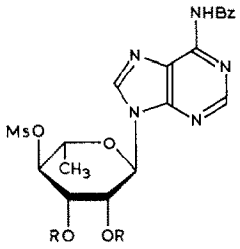
Treatment of **5a** with a slight excess of potassium *tert*-butoxide in *tert*-butyl alcohol effected epoxide formation, without amide hydrolysis, and gave **6**. The structure of **6**, expected on chemical grounds, was confirmed by the n.m.r. data



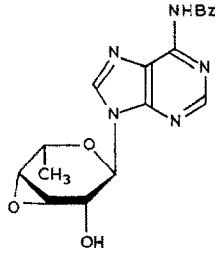
1 R = Ac
2a R = H
2b R = Me_3Si



3 R = H
4 R = Ms



5a R = H
5b R = Me_3Si



6

TABLE I

N.M.R. DATA FOR THE CARBOHYDRATE MOIETIES OF **1–6**

Compound	*Chemical shifts (δ)*						*Coupling constants (Hz)*				
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*Me-5*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
1	← 6.14 →		5.57	4.97	4.17	1.36	<2	2	6	6	6
2a	6.07	4.70	← 3.97 →		3.60	1.39	8	3	—	—	6
2b	5.65	4.52	← 3.55 →			0.98	7	2	—	—	6
3	6.10	4.90	4.65	← 3.60 →		1.17	4	6	—	—	6
4	6.27	4.96	5.20	4.50	3.80	1.20	2	6	7	10	6
5a	6.20	← 4.70 →		4.30	3.37	1.53	8	3	—	—	6
5b	5.80	4.50	← 4.00 →			1.15	7	3	—	—	6
6	5.80	4.78	3.68	3.52	4.43	1.38	8	2	4	3	6

(Table I). The quartets at 3.52 and 3.68 p.p.m. were assigned to the epoxide hydrogens H-3′,4′, and the $J_{2',3'}$ and $J_{4',5'}$ values accord[12,13] with a *cis* relationship and hence the *talo* configuration. The $J_{1',2'}$ value of 8 Hz corresponds[14] to a dihedral angle of 153°, suggesting that **6** has a half-chair conformation with O-5′ above the plane of the molecule and the aglycon equatorial.

The $J_{1',2'}$ values (8 Hz) of **2a** and **5a** indicate H-1′,2′ to be axial, in contrast to **1** ($J_{1',2'}$ <2 Hz) where HO-2,3 are substituted. In order to determine if this reflects a solvent effect (Me_2SO), the trimethylsilylated derivatives **2b** and **5b** were prepared. In acetonitrile-d_3, the $J_{1',2'}$ value for each of these compounds was 7 Hz, corroborating the conformational inversion. Although no explanation can be offered so far, this finding also serves to confirm the α configuration of **1**.

EXPERIMENTAL

Reactions were monitored by t.l.c. on silica gel (Ready-Foils, F 1500, Schleicher & Schüll) with ethyl acetate–ethanol mixtures: *A*, 4:1; *B*, 1:1. Evaporations were performed under reduced pressure at 40° unless otherwise noted. N.m.r. data were obtained for solutions in acetonitrile-d_3 (internal Me_4Si) with a Varian T60 instrument; $(CD_3)_2SO$ was used for **2a** and **5a**, and chloroform was used as standard for **2b** and **5b**. The silylations of **2a** and **5a** were carried out in dichloromethane with the chlorotrimethylsilane–triethylamine system. The chromatographically pure compounds obtained after the usual work-up were used for the n.m.r. experiments, without isolation. Melting points are uncorrected. Elemental analyses were made at the "Service Central de microanalyse du C.N.R.S." (Vernaison, France).

*6-Benzoyl-9-(2,3,4-tri-*O*-acetyl-α-*L*-rhamnopyranosyl)adenine* (**1**). — *N*-Benzoyladenine[15] (7.9 g, 33 mmol), dried by azeotropic distillation of benzene, was suspended in dichloroethane (100 mL). Hexamethyldisilazane (13.8 mL, 2 equiv.) and chlorotrimethylsilane (0.83 mL, 0.2 equiv.) were added. The mixture was boiled under reflux until dissolution was complete (~1 h), and then cooled and concentrated to a thick syrup that was treated with a solution of tetra-*O*-acetyl-α-L-rhamnose (10 g, 30 mmol) and stannic chloride (5.3 mL, 1.5 equiv.) in dichloroethane (100 mL). The solution was stirred and boiled under reflux with the exclusion of moisture for 2 h, cooled, diluted with dichloroethane (400 mL), and cautiously neutralised with sodium hydroxide (6.3 g/10 mL of water). The resulting suspension was filtered through Celite, dried (Na_2SO_4), and concentrated. The product crystallised from methanol–water, to yield **1** (9.8 g, 64%), m.p. 125°, $[\alpha]_D$ −35° (*c* 0.1, methanol), R_F 0.63 (solvent *A*), λ_{max} 280 nm (ε 24,000; pH 7).

Anal. Calc. for $C_{24}H_{25}N_5O_8 \cdot 0.33\ H_2O$: C, 55.71; H, 4.96; N, 13.54. Found: C, 55.78; H, 5.06; N, 13.27.

*6-Benzoyl-9-α-*L*-rhamnopyranosyladenine* (**2a**). — A suspension of **1** (10 g) in ammonium hydroxide (200 mL; d, 0.9) and water (200 mL) was stirred for 30 min at room temperature, during which dissolution occurred. Ammonia was evaporated under reduced pressure and the temperature was then raised to 40–50° to evaporate

the water. The product crystallised from ethanol (slightly acidified with acetic acid), to yield **2** (4 g, 53%), m.p. 132–135°, $[\alpha]_D$ −25° (*c* 0.1, methanol), R_F 0.57 (solvent *B*), λ_{max} 280 nm (ε 23,000; pH 7).

Anal. Calc. for $C_{18}H_{19}N_5O_5 \cdot 0.66\ H_2O$: C, 54.41; H, 5.12; N, 17.63. Found: C, 54.42; H, 5.35; N, 16.54.

6-Benzoyl-9-(2,3-O-isopropylidene-α-L-rhamnopyranosyl)adenine (**3**). — A suspension of **2a** (4 g, 10 mmol) in acetone (200 mL), 2,2-dimethoxypropane (40 mL), and toluene-*p*-sulfonic acid (2.4 g, 1.3 equiv.) was stirred at room temperature until dissolution was complete (30 min), and then treated with triethylamine (2 mL) and concentrated. A solution of the residue in ethyl acetate was washed twice with water, dried, and concentrated, and the residue was crystallised from methylene chloride, to yield **3** (3.5 g, 79%), m.p. 119–122°, $[\alpha]_D$ −15° (*c* 0.1, methanol), R_F 0.55 (solvent *A*), λ_{max} 280 nm (ε 25,000: pH 7).

Anal. Calc. for $C_{21}H_{23}N_5O_5 \cdot 0.33\ H_2O$: C, 58.47; H, 5.49; N, 16.24. Found: C, 58.31; H, 5.54; N, 16.08.

6-Benzoyl-9-(2,3-O-isopropylidene-4-O-mesyl-α-L-rhamnopyranosyl)adenine (**4**). — To a solution of **3** (5 g, 11.8 mmol) in methylene chloride (50 mL) and triethylamine (5 mL) was slowly added methanesulfonyl chloride (1.6 mL, 1.8 equiv.). The mixture was stored at room temperature for 30 min, washed with cold, saturated, aqueous sodium hydrogencarbonate, dried, and concentrated. The residue was crystallised from methanol and water, to yield **4** (4.7 g, 80%), m.p. 120°, $[\alpha]_D$ −15° (*c* 0.1, methanol), R_F 0.65 (solvent *A*), λ_{max} 280 nm (ε 22,000; pH 7).

Anal. Calc. for $C_{22}H_{25}N_5O_7S \cdot 0.33\ H_2O$: C, 51.87; H, 5.04; N, 13.75. Found: C, 51.86; H, 5.00; N, 13.08.

6-Benzoyl-9-(4-O-mesyl-α-L-rhamnopyranosyl)adenine (**5a**). — A solution of **4** (3 g, 6 mmol) in trifluoroacetic acid and methanol (20 mL, 9 : 1) was stored for 10 min at room temperature and then concentrated. The product was precipitated with ether, decanted, and washed several times with ether, to yield **5** (2.4 g, 85%), m.p. 130–132°, $[\alpha]_D$ −30° (*c* 0.1, methanol), R_F 0.75 (solvent *B*), λ_{max} 280 nm (ε 20,000; pH 7).

Anal. Calc. for $C_{19}H_{21}N_5O_7S \cdot 0.5\ CF_3CO_2H$: C, 46.15; H, 4.14; N, 13.46. Found: C, 46.27; H, 4.59; N, 13.19.

9-(3,4-Anhydro-α-L-talopyranosyl)-6-benzoyladenine (**6**). — A suspension of **5a** (2 g, 4.3 mmol) in *tert*-butyl alcohol (100 mL) containing potassium *tert*-butoxide (0.6 g, 1.25 equiv.) was stirred for 4 h at room temperature, neutralised with carbon dioxide, filtered through Celite, and concentrated. The residue was extracted with methylene chloride, the extract was washed with water and concentrated, and the residue was crystallised from ethanol–water, to yield **6** (1 g, 66%), m.p. 176° (dec.), $[\alpha]_D$ −25° (*c* 0.05, methanol), R_F 0.64 (solvent *B*), λ_{max} 280 nm (ε 14,000; pH 7).

Anal. Calc. for $C_{18}H_{17}N_5O_4 \cdot 0.5\ H_2O$: C, 57.45; H, 4.79; N, 18.62. Found: C, 57.58; H, 4.97; N, 18.17.

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